Identification and management of opioid-induced neurotoxicity in older adults

Bradley Godwin MD FRCPC Chris Frank MD CCFP(COE)(PC) FCFP Frank Molnar MSc MDCM FRCPC
Derek Dyks RPh BScPharm Ripa Akter MD FRCPC

Clinical question

What are the symptoms of opioid-induced neurotoxicity, and how can I avoid this often unrecognized and serious adverse drug reaction (ADR)?

Bottom line

Canada is the second-largest per capita consumer of opioids in the world.[1] Canadians who are 65 years or older have a higher likelihood of taking opioid therapy on a long-term basis than all other age groups.[2] Opioids are associated with well-known side effects such as constipation, nausea, dizziness, sedation, delirium, and falls. Older adults are at greater risk of ADRs owing to drug-drug interactions, comorbidity, and age-related physiologic changes. This paper summarizes an article published in the *Canadian Geriatrics Society Journal of CME* on opioid-induced neurotoxicity, which is a commonly missed ADR.[3]

Evidence

- A Cochrane review found a statistically significant 42% higher risk of any adverse event and a statistically significant 175% increased risk of serious adverse events associated with medium- and long-term opioid use for treating chronic noncancer pain compared with placebo.[4]
- Opioid-induced neurotoxicity presents with a range of symptoms including hypersomnolence, delirium, hallucinations, allodynia (pain from a stimulus that does not normally provoke pain), hyperalgesia (abnormally increased sensitivity to pain), myoclonus, tremor, and seizures.[5,6]

Approach

Chronic pain is associated with considerable morbidity in older adults, including reduced quality of life, social withdrawal, depression, and disability.[7] While opioids may be an appropriate approach for some older adults, clinicians should remain sensitized to the following risk factors.

Age-related physiologic changes increase the risk of opioid-related ADRs. Decreased renal function with age and illness impairs the excretion of active opioid metabolites; the greater the dependence on renal clearance of a prescribed opioid or active metabolites, the greater the impact on the tolerability of the specific agent. A recent review on opioid management in older adults with chronic kidney disease recommended hydromorphone, buprenorphine, and fentanyl as the safest opioids in terms of ADRs.[8] It is important to note that fentanyl is not a first-line therapy.

First-pass metabolism can be substantially decreased in older adults; medications with substantial first-pass metabolism (eg, morphine) will reach higher levels in the elderly.

Among older adults, enhanced pharmacodynamic sensitivity (ie, more pronounced effects compared with those that younger people experience while taking equivalent doses) is seen with all opioids. As a result, longer pain relief can be achieved at lower doses.[9]

Drug-drug interactions increase the risk of opioid-related ADRs. Cytochrome P450 (CYP) enzymes are among the principal pathways of drug metabolism for opioids. Substantial metabolism via CYP pathways will predispose older adults to drug-drug interactions and therefore to potential toxicity or decreased efficacy depending on the interacting drugs and the nature of the interaction. In general, hydromorphone has minimal drug-drug interactions.

Morphine primarily undergoes phase II metabolism via the UGT2B7 isoenzyme; however, CYP3A4 inhibitors (amiodarone, diltiazem, verapamil, grapefruit juice, antifungals) can theoretically increase morphine bioavailability, leading to heightened opioid effects. Alternatively, CYP3A4 inducers (anticonvulsants such as phenytoin) may reduce morphine bioavailability.

Codeine has a high potential for drug-drug interactions owing to its metabolism by both CYP2D6 and CYP3A4 isoenzymes. Codeine is converted to morphine via O-demethylation, which is catalyzed by CYP2D6. There is strong evidence that CYP2D6 inhibitors (quinidine, bupropion, fluoxetine, paroxetine) inhibit morphine production and its opioid effects. Codeine is also metabolized to inactive norcodeine via CYP3A; there is some evidence that CYP3A4 inhibitors increase codeine and subsequent morphine bioavailability.

For more information, including the pharmacokinetic properties of various opioids, see Table 1 in the Canadian Geriatrics Society (CGS) journal article.[3]

Implementation

Since opioid-induced neurotoxicity presents with a range of symptoms (ie, hypersomnolence, delirium, hallucinations, allodynia, hyperalgesia, myoclonus, tremor, seizures[5,6]), it can be challenging to diagnose because it can be misinterpreted as disease progression in patients with cancer

or who are palliative, or it can be attributed mistakenly to other neurologic causes. Neurotoxicity can occur with any opioid, but it is most commonly associated with those that form active metabolites (meperidine, morphine, oxycodone, and hydromorphone).[6,10] Risk factors for opioid-induced neurotoxicity include high opioid dosage, dehydration, renal failure, infection, and advanced age (owing to an increased risk of metabolite accumulation).

A multimodal and multidisciplinary approach is essential to addressing the multifaceted nature of chronic pain, as summarized in Table 2 in the CGS article.[3] If opioids are prescribed after optimizing nonpharmacologic and nonopioid pharmacologic therapy, it is important to routinely reassess their efficacy and monitor for non-neurologic ADRs and opioid-induced neurotoxicity. Physicians should proactively counsel patients who are at risk of dehydration (for reasons such as having inadequate oral fluid intake or taking drugs that can result in volume depletion or cause renal impairment) about opioid-induced neurotoxicity.

Opioid-induced neurotoxicity is managed with dose reduction or discontinuation of the drug, opioid rotation (ie, switching to an alternative opioid), hydration, and the correction of underlying precipitants, such as renal impairment. If performing an opioid rotation, it is recommended to reduce the calculated equianalgesic dose of the new opioid by 25% to 50% to avoid inadvertent overdose (see Table 3 in the CGS article).[3] Rotation involving transdermal fentanyl requires close monitoring as wide variations of dosing equivalencies have been reported. The use of parenteral hydration (subcutaneous or intravenous) should be considered where feasible.

Dr Bradley Godwin is a geriatric medicine resident in the Department of Medicine at the University of Ottawa in Ontario. **Dr Chris Frank** is a family physician specializing in care of the elderly and palliative care at Queen's University in Kingston, Ont. **Dr Frank Molnar** is a specialist in geriatric medicine practising in the Department of Medicine at the University of Ottawa and at the Ottawa Hospital Research Institute. **Derek Dyks** is Pharmacy Specialist at the Ottawa Hospital. **Dr Ripa Akter** is a geriatrician in the Department of Medicine at the University of Ottawa.

Competing interests
None declared

References

1. *Narcotic drugs 2017. Estimated world requirements for 2018. Statistics for 2016.* Vienna, Austria: International Narcotics Control Board; 2017. Available from: **https://www.incb.org/incb/en/narcotic-drugs/Technical_Reports/2017/narcotic-drugs-technical-report-2017.html**. Accessed 2022 Feb 28.
2. *Opioid prescribing in Canada. How are practices changing?* Ottawa, ON: Canadian Institute for Health Information; 2019. Available from: **https://www.cihi.ca/sites/default/files/document/opioid-prescribing-canada-trends-en-web.pdf**. Accessed 2022 Feb 28.
3. Godwin B, Dyks D, Akter R. Tolerability of opioids in older adults: focus on neurotoxicity. *Can Geriatr Soc J CME* 2021;11(2). Epub 2021 Dec 15. Available from: **https://canadiangeriatrics.ca/2021/12/tolerability-of-opioids-in-older-adults-focus-on-neurotoxicity/**. Accessed 2022 Jan 5.
4. Els C, Jackson TD, Kunyk D, Lappi VG, Sonnenberg B, Hagtvedt R, et al. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane reviews. *Cochrane Database Syst Rev* 2017;(10):CD012509.
5. Martin EJ, Vaughan CL, Atayee R, Hirst JM, O'Donnell K, Edmonds KP. Hydromorphone-induced chorea as an atypical presentation of opioid neurotoxicity: a case report and review of the literature. *Palliat Med* 2018;32(9):1529-32. Epub 2018 Jul 13.
6. Lim KH, Nguyen NN, Qian Y, Williams JL, Lui DD, Bruera E, et al. Frequency, outcomes, and associated factors for opioid-induced neurotoxicity in patients with advanced cancer receiving opioids in inpatient palliative care. *J Palliat Med* 2018;21(12):1698-1704. Epub 2018 Sep 27.
7. Papaleontiou M, Henderson CR Jr, Turner BJ, Moore AA, Olkhovskaya Y, Amanfo L, et al. Outcomes associated with opioid use in the treatment of chronic noncancer pain in older adults: a systematic review and meta-analysis. *J Am Geriatr Soc* 2010;58(7):1353-69. Epub 2010 Jun 1.
8. Owsiany MT, Hawley CE, Triantafylidis LK, Paik JM. Opioid management in older adults with chronic kidney disease: a review. *Am J Med* 2019;132(12):1386-93. Epub 2019 Jul 8.
9. Naples JG, Gellad WF, Hanlon JT. The role of opioid analgesics in geriatric pain management. *Clin Geriatr Med* 2016;32(4):725-35. Epub 2016 Aug 9.
10. Gallagher R. Opioid-induced neurotoxicity. *Can Fam Physician* 2007;53:426-7.

This article is eligible for Mainpro+ certified Self-Learning credits. To earn credits, go to **https://www.cfp.ca** and click on the Mainpro+ link.
Can Fam Physician 2022;68:269-70. DOI: 10.46747/cfp.6804269
La traduction en français de cet article se trouve à **https://www.cfp.ca** dans la table des matières du numéro **d'avril 2022** à la **page e118**.